SECURITY CLASSIFICATION OF THIS PAGE

DTIC ELECTE JAN 22 1991 S D

REPORT DOCUMENTATION PAGE

AD-A231 379

1a. REPORT SECURITY CLASSIFICATION: (U)	1b. RESTR: N..
2a. SECURITY CLASSIFICATION AUTHORITY: NA	3. DISTRIBUTION/AVAILABILITY OF REPORT: DISTRIBUTION UNLIMITED
2b. DECLASSIFICATION/DOWNGRADING SCHEDULE: NA	
4. PERFORMING ORGANIZATION REPORT NUMBER(S): New England Medical Center Hospitals, Inc.	5. MONITORING ORGANIZATION REPORT NUMBER(S): NA
6a. NAME OF PERFORMING ORGANIZATION: New England Medical Center Hospitals, Inc.	6b. OFFICE SYMBOL (If applicable): NA
7a. NAME OF MONITORING ORGANIZATION: Office of Naval Research	
6c. ADDRESS (City, State, and ZIP Code): New England Medical Center Hospital, Inc. Box 817, 750 Washington St. Boston, MA 02111	7b. ADDRESS (City, State, and ZIP Code): 800 N. Quincy Street Arlington, VA 22217-5000
8a. NAME OF FUNDING/SPONSORING ORGANIZATION: Office of Naval Research	8b. OFFICE SYMBOL (If applicable): ONR
9. PROCUREMENT INSTRUMENT IDENTIFICATION NUMBER: N00014-90-5-1560	
8c. ADDRESS (City, State, and ZIP Code): 800 N. Quincy Street Arlington, VA 22217-5000	10. SOURCE OF FUNDING NUMBERS: PROGRAM ELEMENT NO: 61153N; PROJECT NO: RR04108; TASK NO: 444r003--01; WORK UNIT ACCESSION NO:

11. TITLE (Include Security Classification): The development of a mathematical description of the olfactory bulb, validated with intracellular and voltage-sensitive dye recordings: (U)

12. PERSONAL AUTHOR(S): Kauer, John S.

13a. TYPE OF REPORT	13b. TIME COVERED	14. DATE OF REPORT (Year, Month, Day)	15. PAGE COUNT
Annual	FROM 1/90 TO 1/91	Jan. 16, 1991	15

16. SUPPLEMENTARY NOTATION: N/A

17. COSATI CODES			18. SUBJECT TERMS (Continue on reverse if necessary and identify by block number)
FIELD	GROUP	SUB-GROUP	
08			Computational modelling; olfactory system; salamander; odors

19. ABSTRACT (Continue on reverse if necessary and identify by block number)

The objective of this work is to develop a detailed mathematical description of the function of the olfactory epithelium and bulb in the tiger salamander, an animal from which we, and others, have obtained substantial morphological, biochemical, physiological and behavioral information. This project focuses especially on incorporating the information available about the numbers of cells, their connectivities, and the single cell and ensemble physiological responses using voltage-sensitive dye fluorescence, into the model.

20. DISTRIBUTION/AVAILABILITY OF ABSTRACT	21. ABSTRACT SECURITY CLASSIFICATION
X UNCLASSIFIED/UNLIMITED ☐ SAME AS RPT ☐ DTIC USERS	(U)
22a. NAME OF RESPONSIBLE INDIVIDUAL: Dr. Ogor Vodyanoy	22b. TELEPHONE (Include Area Code): 703-696-4056 / OFFICE SYMBOL: ONR

DD Form 1473, JUN 86 — Previous editions are ... — SECURITY CLASSIFICATION OF THIS PAGE

S/N 0102-LF-014-6603

John S. Kauer SS#133-34-4857

PROGRESS REPORT ON CONTRACT N00014-90-J-1560

CONTRACT TITLE:

Development of a Mathematical Description of the Olfactory Bulb, Validated with Intracellular and Voltage-Sensitive Dye Recordings.

RESEARCH OBJECTIVE:

The objective of this work is to develop a detailed mathematical description of the function of the olfactory epithelium and bulb in the tiger salamander, an animal from which we, and others, have obtained substantial morphological, biochemical, physiological and behavioral information. This project focuses especially on incorporating the information available about the numbers of cells, their connectivities, and the single cell and ensemble physiological responses using voltage-sensitive dye fluorescence, into the model.

ABSTRACT

The encoding and neural integration of molecular signals are processes that underly all nervous system functions and are crucial for an organism's ability to recognize chemical compounds in the environment. As a sensitive, broad-spectrum molecular (odor) detector, the sense of smell serves as a model system for studying neuronal, molecular receptors and information processing in synaptic circuits. Central nervous system regions involved in olfaction mediate life-sustaining behaviors such as food-finding and mate recognition in animals and are the sites of devastating pathologies that include epilepsy, schizophrenia, and Alzheimer's disease in humans. Despite the clinical and basic neurobiological importance of this system, little is known about how molecular, odor information is acquired, processed and integrated by the brain.

The long-term aim of this research is to understand how odors are encoded and integrated in the olfactory pathway. To do this, one must study how olfactory neurons function both as single elements and as cooperative members of synaptic networks when stimulated with odors. Our approach has been to develop an animal model (the tiger salamander) which can be electrophysiologically studied after stimulation using controlled odor delivery and from which odor-guided behavior can be obtained. In single cell recording studies this preparation has permitted precise correlation of odors with extra- and intracellular receptor and mitral/tufted unit responses. For recording from cell assemblies and networks we have used the salamander to develop a new method for dynamic recording from the olfactory epithelium and bulb using real-time imaging of voltage-sensitive dye fluorescence.

We have several on-going studies in which we are investigating single cell and ensemble responses from the olfactory pathway. The present report describes the development of a mathematical model of the anatomical properties and physiological events we have observed using the approaches described above. In the course of developing this model, we have found that the process of having to minutely characterize each and every neuronal event in formal mathematical terms has greatly clarified our conceptualization of these processes, specifically highlighting those data which are lacking and emphasizing those events which have been poorly thought through. We think that the ability to develop such a formal description of neurophysiological events in the olfactory bulb in the context of being able to actually record from single cells and the overall network, provides a unique opportunity to validate the mathematical models we, and others, have developed.

METHODS

We use a series of linked differential equations which describe the responses in cells making up a somewhat simplified synaptic network representing the olfactory epithelium and bulb of the salamander. The program is written in 'C' and has been run on a variety of computational platforms, including a 16MHz 80386 with a 80387 math coprocessor, a 33 MHz 80386 with a

Weitek 3167 math coprocessor, and most recently (and most efficiently) a 33 MHz 80486 with a 40 MHz Microway i860 co-processor board.

We have included 1000 receptor cells, 20 primary dendrites of mitral cells in the glomeruli (hereafter referred to as glomerular elements), 10 periglomerular cells, 10 mitral cells, and 1000 granule cells (see Fig. 1) into the model. There are more 'glomerular' elements than 'mitral' elements because, in the salamander, mitral/tufted cells have more than one primary dendrite. Although, at this stage of development, the number of mitral cells is small, the use of numbers in these ratios allows us to approximate the patterns and degrees of convergenence and divergence among the various cell types. The most recent implementation, on the i860 co-processor, is approximately 20 times faster than the implementation on the 33 MHz Weitek chip, thus allowing us to potentially enlarge the model at least 5 times and still be able to carry out computations representing 2 seconds of real time in 2-3 minutes of computer time. We believe rapid computation of the model's behavior is critical for effectively examining large numbers of parameter permutations.

Activity in each cell is represented as a value in a matrix representing membrane potential (e.g. the membranc potential in the *n*th receptor cell is designated 'rec[n]'). We use membrane potential as the response parameter of each cell because we can measure this directly in our intracellular and voltage-sensitive dye recordings and because it effectively represents all events ocurring in the cells, not just those associated with action potentials. Thus there is a matrix for each cell type of the following sizes: rec[1000], glom[20], pg[10], mit[10], grl[1000].

In addition to these 'response matrices', we have set up 'connectivity matrices' which define the connections between cells, for example between the *n*th receptor cell and *j*th glomerular element or the *k*th periglomerular cell and *j*th glomerular element. These are two dimensional matrices in the form of rec_glom[recnum][glomnum], to indicate the magnitude and sign of the connections between, in this case, any one receptor cell and any one glomerular element. As an illustration, one might define a strict point-to-point mapping of the first 100 receptor cells onto the first glomerular element, the second 100 receptor cells onto the second glomerular element and so on. Or, more realistically from what we know of the mapping of peripheral receptors onto glomeruli in the salamander, we might connect the first 30 receptor cells to the first glomerular element and the next 60 to each of the other nineteen glomerular elements equally. We are presently in the process of examining the effects of manipulating these kinds of connectivity parameters.

To calculate the membrane potential of a particular mitral cell, for example, we evaluate the magnitudes of the inputs from all cells impinging on that mitral cell, modified by their connectivity coefficients. For a particular receptor to mitral connection, this consists of adding the response of the receptor cell times the strength of its connection. This calculation is also modified by other factors that occur at that site (e.g. synaptic decay constants, whether spikes are elicited, etc.). The calculation is also multiplied by a time step which limits the degree of extrapolation to the next time point. In our calculations this time step is allowed to represent, at most, a real time of 1 ms and is adjusted to become shorter as events change more rapidly (as, for example, during an imposed depolarization, designed to mimic an electric shock stimulus of the receptors). One millisecond seems to be a reasonable time step value for modelling events in salamander neurons since action potentials in this animal last about 10 ms.

In more formal mathematical terms, the manipulations described above are an example of the use of a forward Euler method of numerical integration. For example, to evaluate the mitral/granule reciprocal interaction we let the membrane potential of each cell be represented by a vector; for the granule cell this is G such that:

(1) $G = \{g_0, g_1, \ldots g_i, \ldots g_N\}$

where N_g is the number of granule cells.

In the same way, we let the membrane potential for each mitral cell be represented by another vector M such that:

(2) $M = \{m_0, m_1, \ldots m_i, \ldots m_N\}$

where N_m is the number of mitral cells.

Taking into account, for this example, only the change in membrane potential in these two cell types and a membrane decay time constant for each cell, the membrane potential at time t for granule cell i coupled to mitral cell j, will then be:

$$\frac{dg_i}{dt} = -\frac{1}{\tau_g} g_i + \sum_{j=0}^{N_m} a_{ij} m_j \quad (3)$$

and the membrane potential for mitral cell i coupled to granule cell j will be:

$$\frac{dm_i}{dt} = -\frac{1}{\tau_m} m_i + \sum_{j=0}^{N_g} b_{ij} g_j \quad (4)$$

where τ_m is the membrane decay constant for mitrals

τ_g is the membrane decay constant for granules

b_{ij} is the granule --> mitral coupling coefficient

a_{ij} is the mitral --> granule coupling coefficient.

Such equations along with equivalent ones representing the connectivities, membrane properties, etc. for all of the other cells are integrated using the method described above and equations for all parameters in all cells are calculated for each time step iteration. We generally calculate sufficent numbers of iterations to represent 2 secs of real time. We have approached these equations as an initial value problem, that is we start all membrane potentials at zero and introduce a spontaneous firing rate in each of the cell types. The model is run using an explicit adaptive step-size algorithm which, as mentioned earlier, adjusts the time step size (dt) according to the slope of the function between points; the steeper the slope, the shorter the time step. The model is allowed to first come to a steady state and is then subjected to a simulated stimulus in the form of an electrical or odor-induced depolarization applied to the receptor cells as shown in Figs. 2,3,4 and 6,7.

For reasonable choices of coupling parameters, membrane time constants, firing rates, etc., the model is stable using Euler's integration method, which is, in essence, a linear extrapolation from the present time point to the next one using the slope of the function. We are in the process of evaluating other methods of integration such as, for example, a fourth order Runge-Kutta technique, which examines two points behind and two points ahead of the point of interest, to evaluate differences in efficiency and accuracy among the methods.

RESULTS

The output of the model is displayed in two formats. Fig. 2 shows displays of the values in each cell of the arrays at various times after the beginning of the run (t = xx) in the form of gray scale plots of the matrices. The displays on the left side of the figure represent the values in the receptor cell matrix, with the matrix displayed to schematically represent the actual shape of the ventral receptor sheet in the salamander. The displays on the right side of the figure represent the values in the matrices of the various bulbar components; the periglomerular, glomerular, mitral, and granule elements. The orientation of the bulbar layers in this display approximately conform to their orientation seen real voltage-sensitive dye images. The values in these displays range above and below resting value which is shown by the mid gray value seen uniformly throughout the receptor matrix at t = 530 ms. Gray values lighter than this represent depolarization (white represents spikes), darker grays represent hyperpolarization.

In this trial a simulated electrical stimulus was applied to the locations shown on the

receptor sheet at t = 500 ms (first row, white squares). As shown at t = 530 ms, this stimulus elicited depolarization of periglomerular cells (with spikes) and of glomerular elements. At t = 546 ms depolarization appeared in mitral and granule cells and at t = 580, the granule cells showed widespread depolarization and the mitrals hyperpolarized.

The second display format is shown in Figs. 3,4 and 6,7. These figures show the changes in membrane potential for particular cells as if one were recording from them using an intracellular electrode. Recordings from one receptor cell (of 1000), one periglomerular cell (of 10), one glomerular element (of 20), and one granule cell (of 1000) are shown at the tops of these figures. Simulated recordings from all ten mitrals are shown toward the bottoms of the figures.

In Figs. 3 and 4 a simulated electrical stimulation was applied to receptor cells 300-700 at low and high intensities. With a low intensity, two spikes are elicited from the pg cell, and a single spike is elicited in mitral cells 2-6 followed by a hyperpolarization. Fig. 4 shows that with high intensity stimulation more spikes are elicited from pg's and mitral cells, a spike now appears in the granule cell, and the mitral hyperpolarization is deeper and longer lasting. These simulated responses are to be compared with real intracellular recordings from salamander mitral/tufted cells shown in Fig. 5 (made by K.A. Hamilton in this lab). Notice that in these records, with more intense stimulation, more spikes and a deeper and longer lasting hyperpolarization are elicited.

In Figs. 6 and 7 a simulated, heterogeneously distributed odor stimulation at high and low intensities is applied to the receptor matrix (see display of receptor matrix at bottom left of each fig). Here the responses in the mitral cells are more complex than with electrical stimulation, consisting of brief bursts of spikes, brief, slight hyperpolarizations, long lasting depolarizations, and longer-lasting following hyperpolarizations. With higher intensity odor stimulation there are actually fewer spikes elicited from mitral cells than with the lower intensity. These responses are surprisingly similar to those observed in real intracellular recordings from mitral/tufted cells at different odor intensities as shown in Fig. 8 (made by K.A. Hamilton in this lab) and are consistent with the concept of concentration tuning we had previously developed on the basis of extracellular studies.

We have been greatly encouraged by these results because we initially put into the model parameters that made the most physiological sense in order to get results similar to those we had obtained from the real system under conditions of **electrical stimulation**. Once the model functioned with these parameters we then tested it with simulated odor stimuli and obtained the results shown here **without manipulating the parameters.** That is the model was not setup using knowledge about the odor responses, but only using knowledge about the electrical responses; only then was it tested for its odor responsivity. As one can see by comparing Figs. 6 and 7 with Fig. 8, the similarity is striking.

We now think we have a reasonably good starting model with which to examine the effects of manipulating a wide variety of physiological parameters such as the effects of changing synaptic efficacy using pharmacological agents.

PUBLICATIONS AND REPORTS (Year 1):

Kauer, J.S., Neff, S.R., Hamilton, K.A., Cinelli, A.R. (1991) The Salamander Olfactory Pathway: Visualizing and Modelling Circuit Activity. In: Davis, J. and Eichenbaum, H. (eds.), Olfaction as a Model System for Computational Neuroscience. MIT Press. (in press).

White. J., Neff, S.N. Cinelli, A.R., Kauer, J.S. (1990) Modelling the salamander olfactory bulb: single cell and network interactions. Neurosci. Abst., abstract.

White, J., Neff, S.N., Hamilton, K.A., Kauer, J.S. (1991) A comprehensive model of the peripheral olfactory pathway of the salamander. J. Biophys. (in preparation)

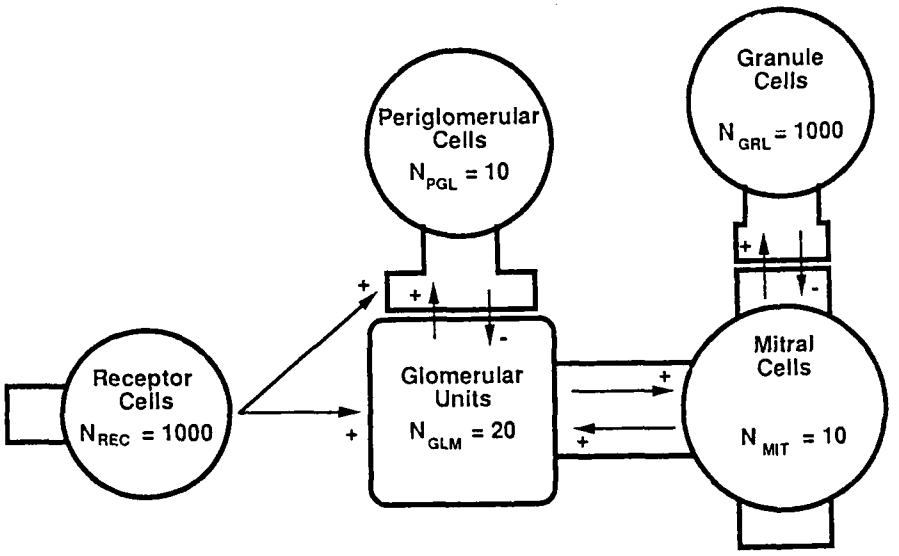
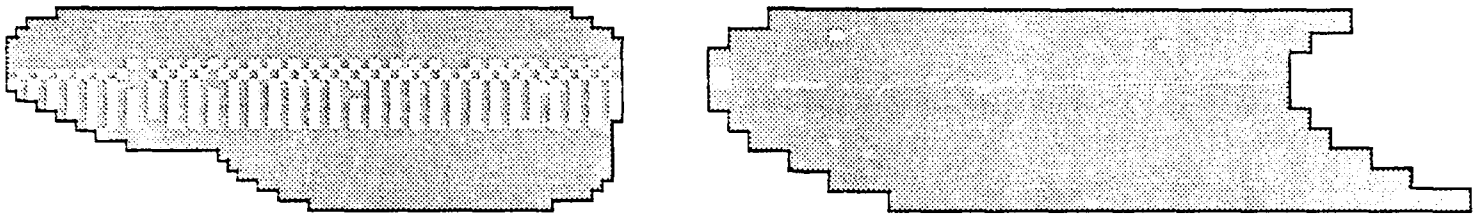
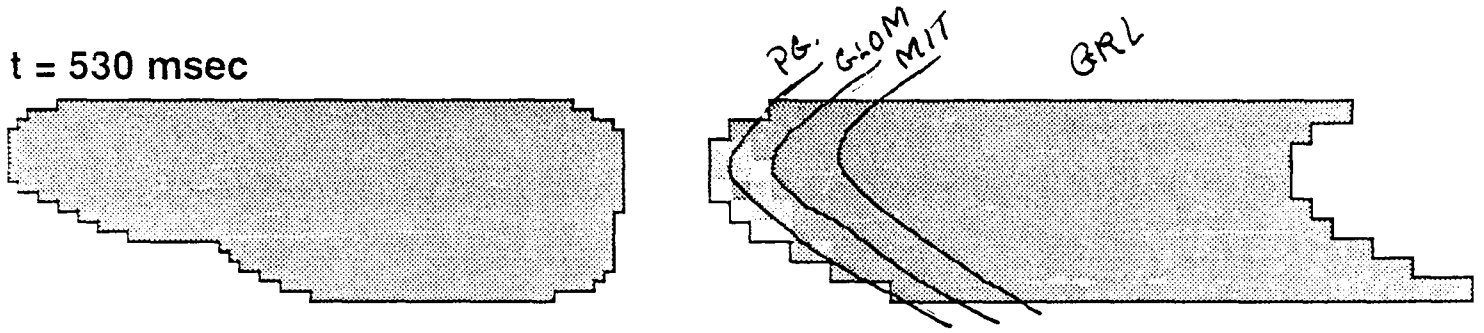

Granule
Cells
N_{GRL} = 1000
Periglomerular
Cells
N_{PGL} = 10
Receptor
Cells
N_{REC} = 1000
Glomerular
Units
N_{GLM} = 20
Mitral
Cells
N_{MIT} = 10
+
-

FIG. 1.

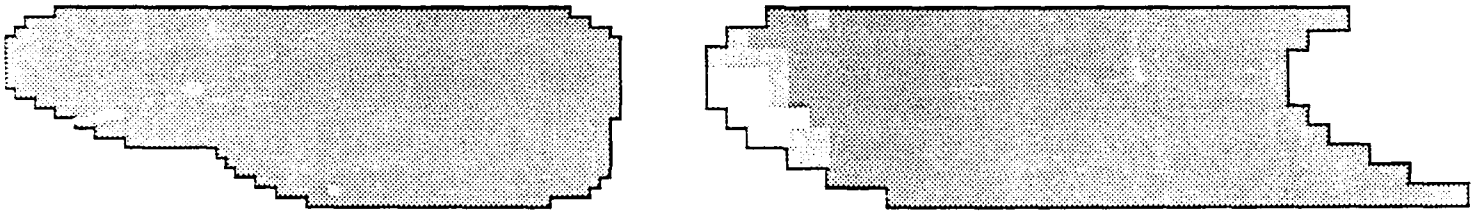
t = 502 msec



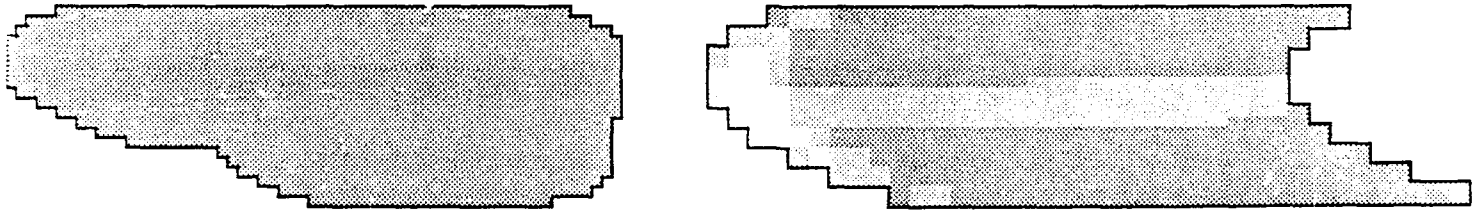
t = 530 msec



t = 534 msec



t = 546 msec



t = 580 msec

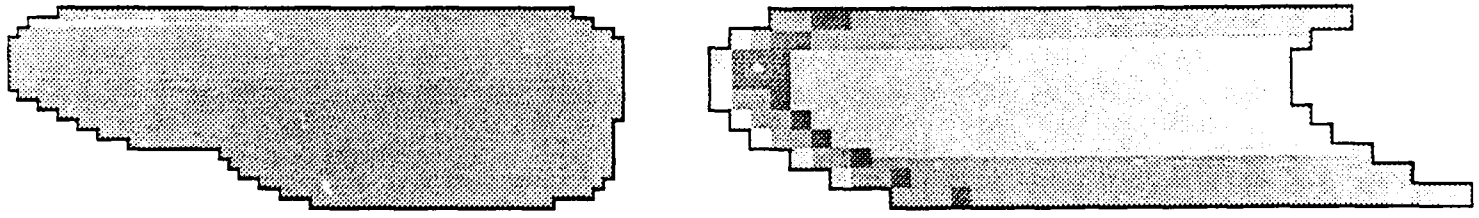


FIG. 2

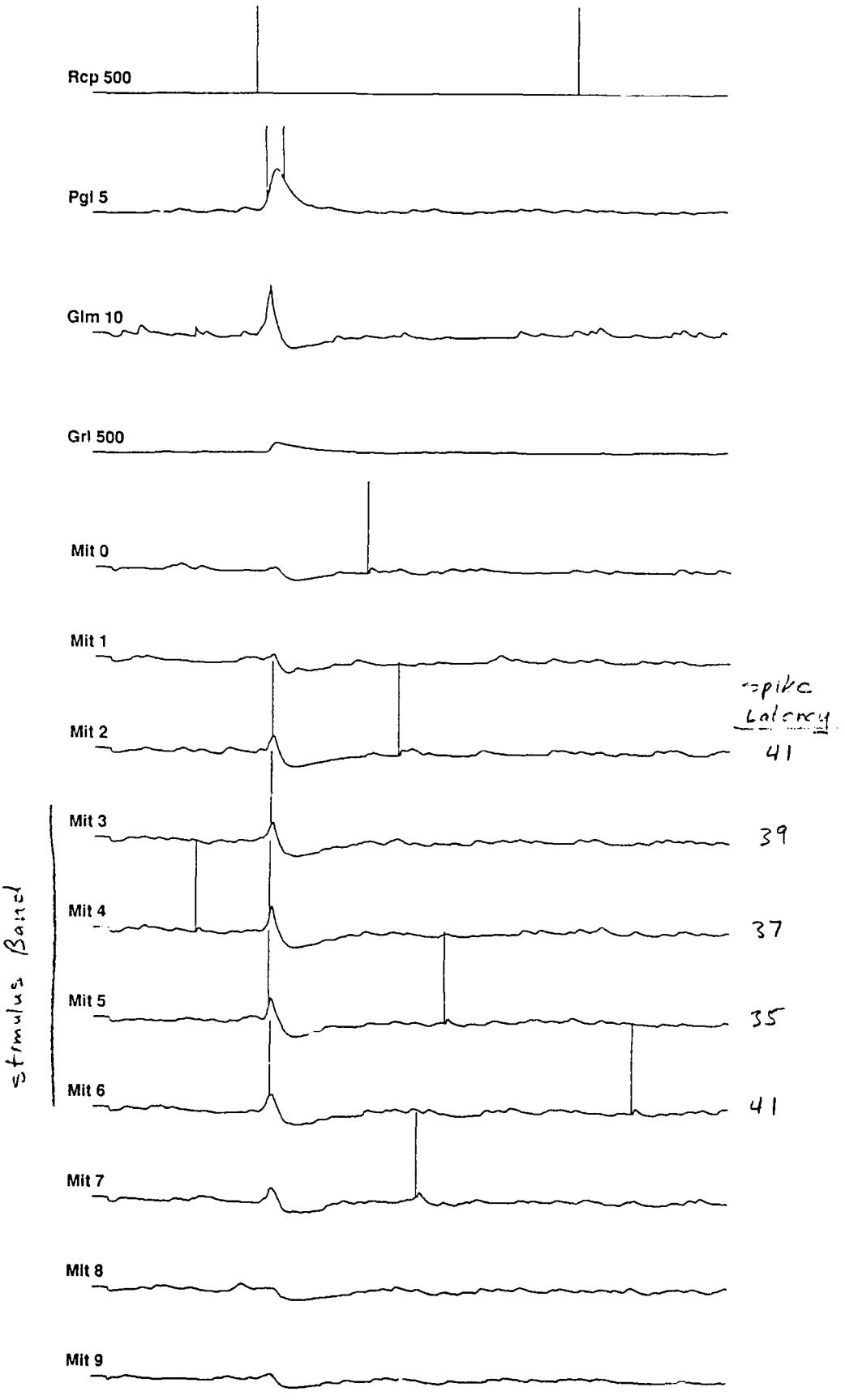

Low Electrical Stimulus Intensity
Rcp 500
Pgl 5
Glm 10
Grl 500
Mit 0
Mit 1
Mit 2
Mit 3
Mit 4
Mit 5
Mit 6
Mit 7
Mit 8
Mit 9
Spike Latency
41
39
37
35
41
Stimulus Band

FIG. 3

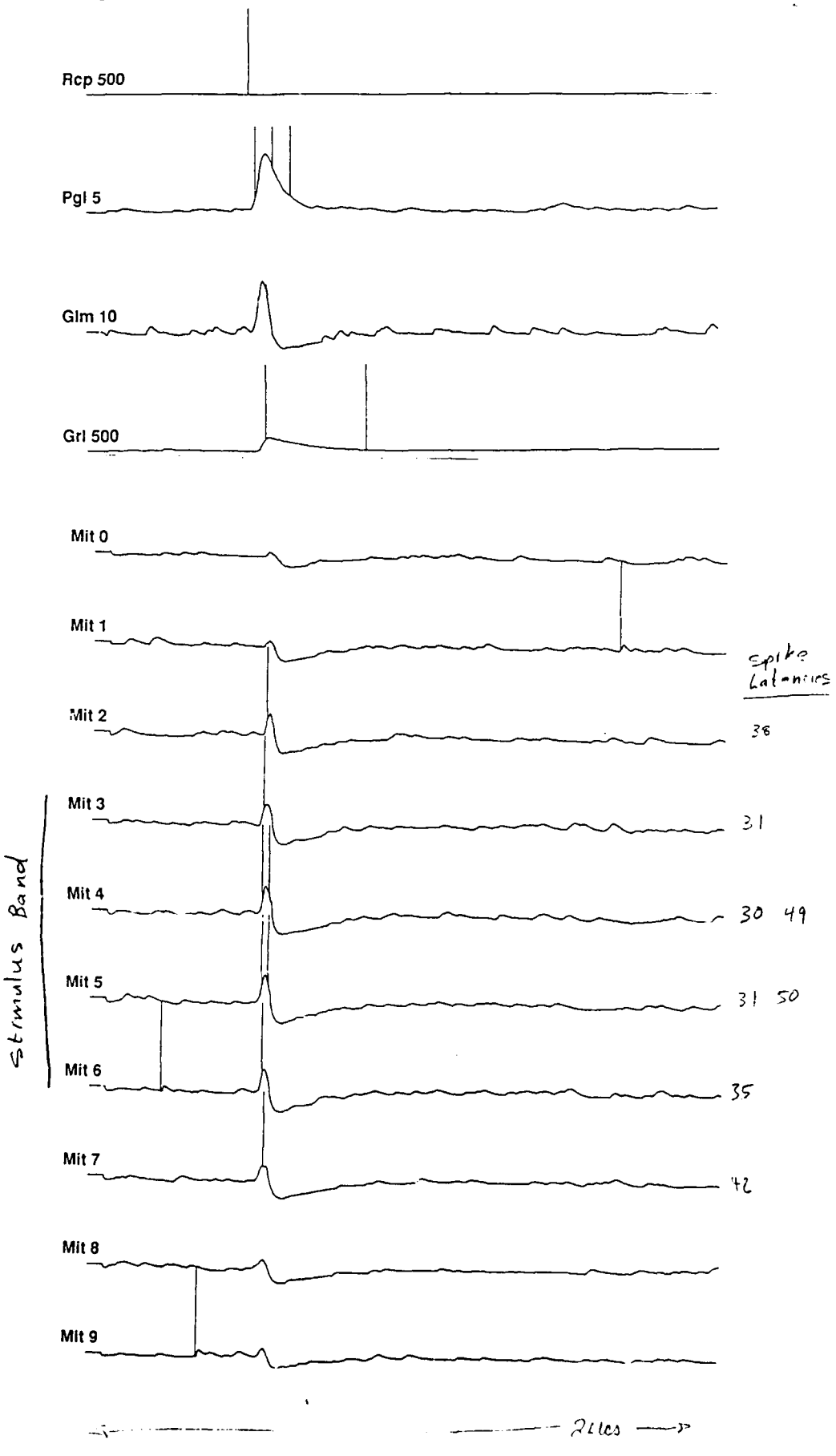

High Electrical Stimulus Intensity
Rcp 500
Pgl 5
Glm 10
Grl 500
Mit 0
Mit 1
Mit 2
Mit 3
Mit 4
Mit 5
Mit 6
Mit 7
Mit 8
Mit 9
Stimulus Band
Spike Latencies
38
31
30 49
31 50
35
42
2 ms

FIG. 4

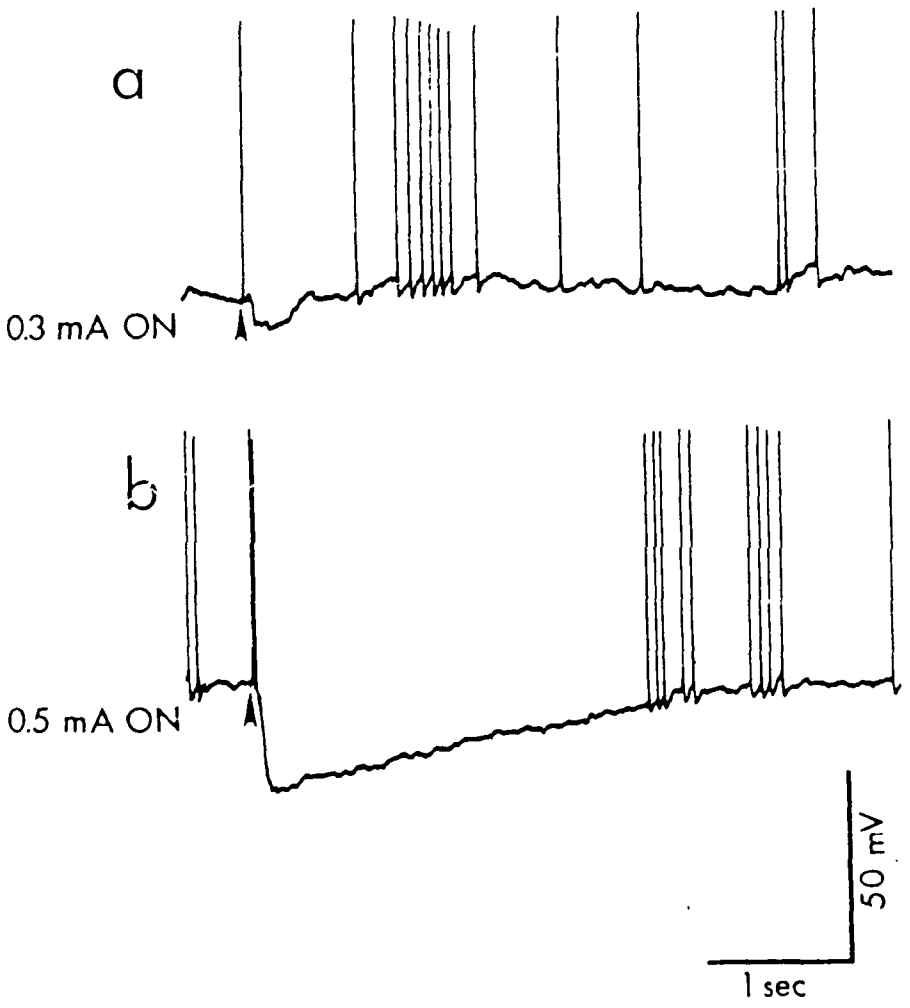


FIG. 5

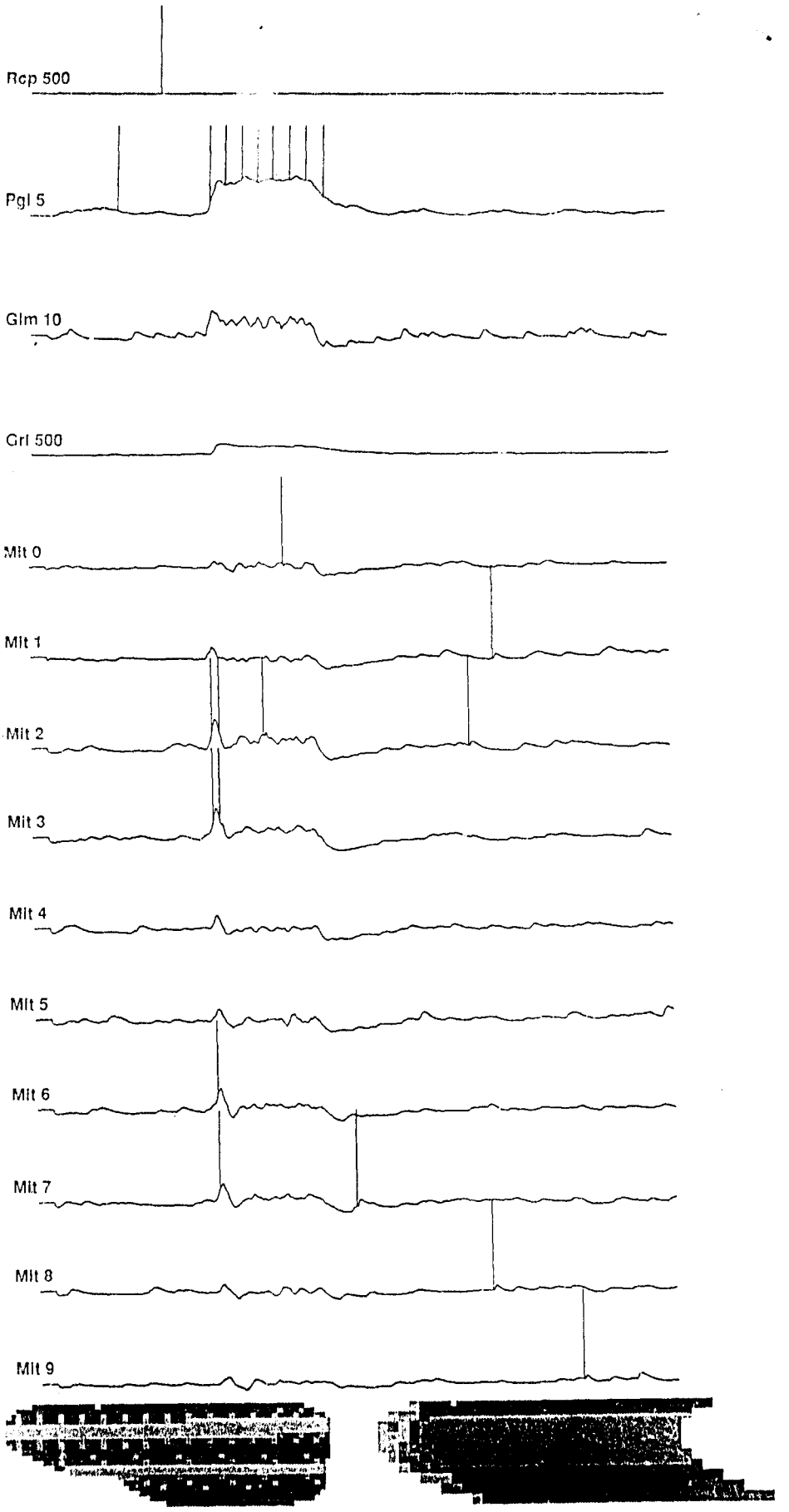


FIG. 6

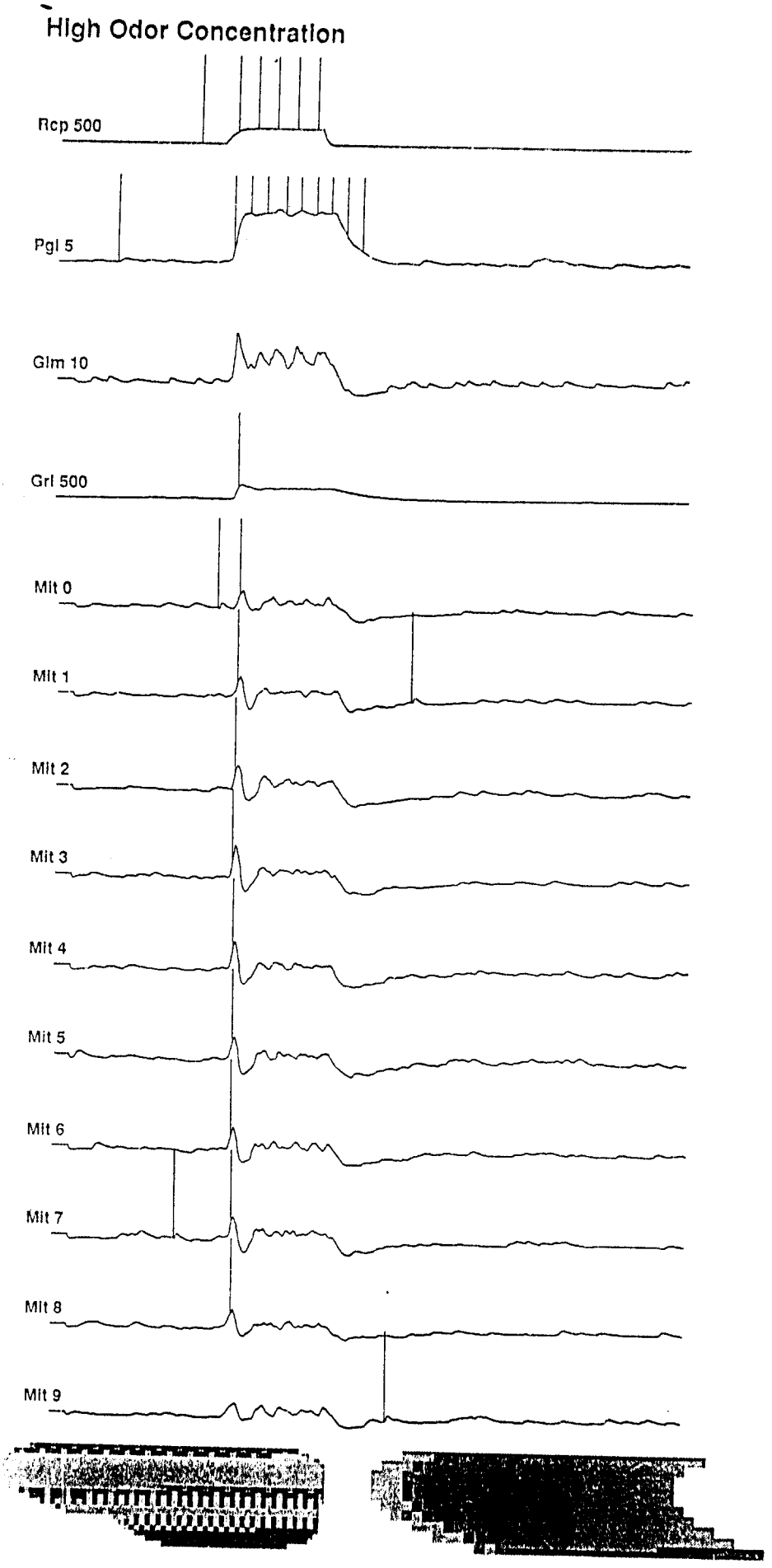


FIG. 7

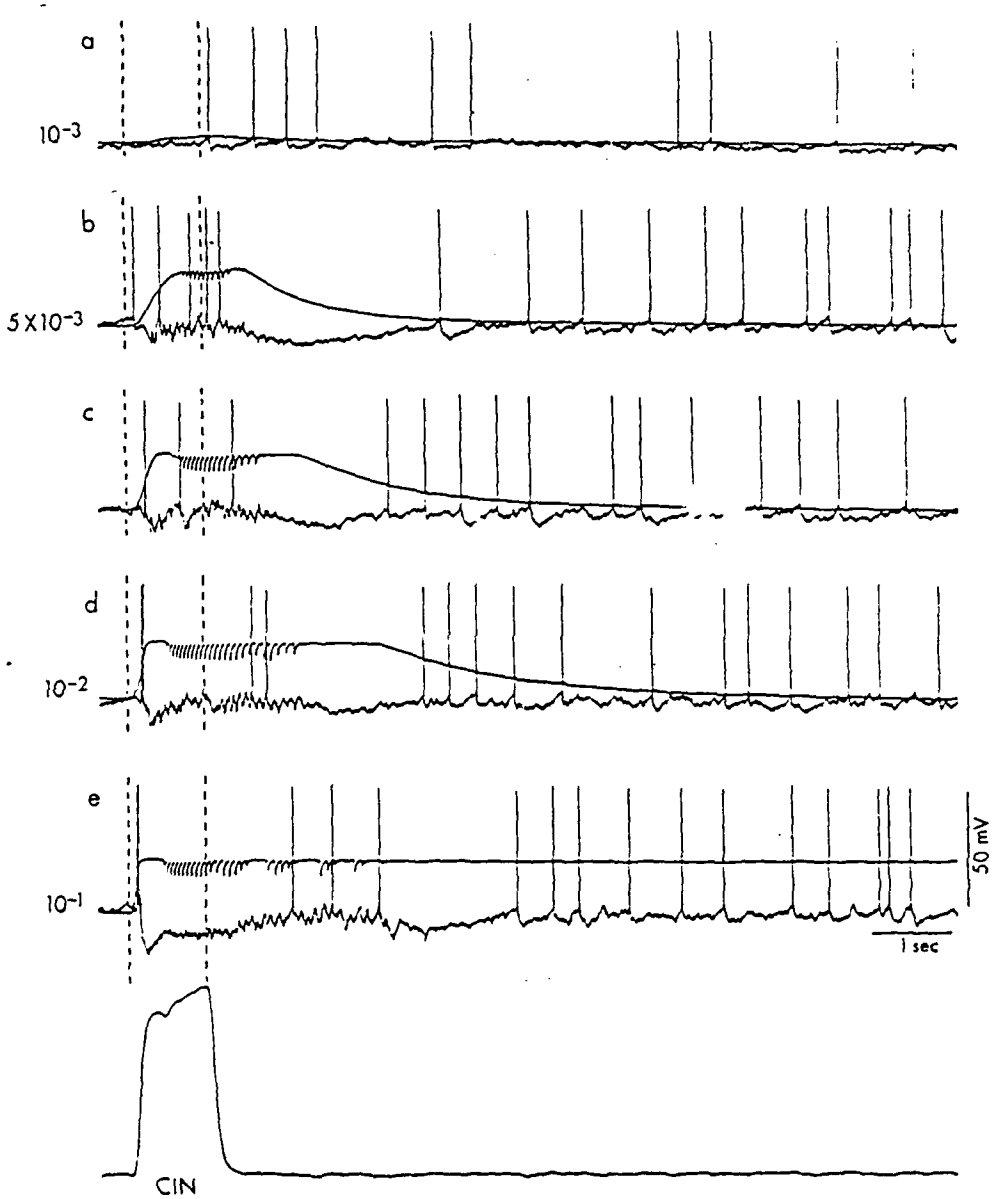


FIG. 8

OLFACTORY DISCRIMINATION PROGRAM

✓ Dr. Barry W. Ache
Whitney Laboratory
University of Florida
9505 Ocean Shore Blvd.
St. Augustine, FL 32086-8623

✓ Dr. Richard C. Bruch
Dept. of Neurobiology & Physiology
Northwestern University
O. T. Hogan Hall
Evanston, IL 60208

✓ Dr. John Caprio
Dept. of Zoology & Physiology
Louisiana State University
Baton Rouge, Louisiana 70803-1725

✓ Dr. Vincent Dionne
Dept. of Pharmacology
M-036, School of Medicine
University of California
La Jolla, CA 92093

✓ Dr. Stuart Firestein
Section of Neuroanatomy
Yale University
School of Medicine
C303 Sterling Hall of Medicine
333 Cedar Street
New Haven, Connecticut 06510

✓ Dr. Stephen P. Fracek, Jr.
Dept. of Biological Sciences
University of North Texas
P.O. Box 5218
Denton, TX 76203-5218

✓ Dr. William F. Gilly
Hopkins Marine Station
Stanford University
Pacific Grove, CA 93950

Dr. John S. Kauer
Dept. of Neurosurgery
New England Medical Center
750 Washington Street
Boston, MA 02111

✓ Dr. Mimi A. R. Koehl
University of California
540 Banway Building
Berkeley, CA 94720

✓ Dr. Michael Leon
Dept. of Psychobiology
University of California
19172 Jamboree
Irvine, CA 92717

✓ Dr. Donal Manahan
Dept. of Biology
Univ. of So. California
University Park
Los Angeles, CA 90089

✓ Dr. Thomas H. Morton
Department of Chemistry
University of California
Riverside, CA 92521-0217

✓ Dr. W. Charles Neely
Department of Chemistry
Auburn University
Auburn, Alabama 36849-3501

✓ Dr. Dennis E. Rhoads
Dept. of Biochemistry
and Biophysics
University of Rhode Island
70 Lower College Road
Kingston, RI 02881

✓ Dr. Jeanette Yen
Marine Science Research
Center
SUNY
Stony Brook, NY 10019

Olfactory Discrimination Program

Final and Technical Reports

ADMINISTRATORS

✓ Dr. Igor Vodyanoy, Code 1141SB (2 copies)
Scientific Officer, Biophysics
Office of Naval Research
800 N. Quincy Street
Arlington, VA 22217-5000

✓ Administrator (2 copies) (Enclose DTIC Form 50)
Defense Technical Information Center
Building 5, Cameron Station
Alexandria, VA 22314

✓ Administrative Contracting Officer
ONR Resident Representative
(address varies - obtain from contract or your business office.

✓ Dr. Randall Alberte, Code 1141MB
Scientific Officer
Office of Naval Research
800 N. Quincy Street
Arlington, VA 22217-5000

✓ Dr. Joel Davis, Code 1142BI
Program Manager, Biological Intelligence
Office of Naval Research
800 N. Quincy Street
Arlington, VA 22217-5000

✓ Program Manager, Code 125
Biological/Human Factors Division
Office of Naval Research
800 N. Quincy Street
Arlington, VA 22217-5000

✓ Program Manager Defense Technical Support
Technology Directorate
Office of Naval Technology, Code 223
800 N. Quincy Street
Arlington, VA 22217-5000

Annual and Final Reports Only (one copy each)

DoD ACTIVITIES

✓ Commander
Chemical and Biological Sciences Division

Research Army Research Office, P.O. Box 1221
Research Triangle Park, NC 27709

Olfactory Discrimination Program

DoD ACTIVITIES (continued)

✓ Head, Biomolecular Engineering Branch
Code 6190
Naval Research Laboratory
Washington, DC 20375

✓ Directorate of Life Sciences
Air Force Office of Scientific Research
Bolling Air Force Base
Washington, DC 20332

✓ Dr. Tove
4300 S. Miami Boulevard
Research Triangle Park, NC 27709

Final and Technical Reports Only

Director, Naval Research Laboratory (6 copies)
Attn: Technical Information Division, Code 2627
Washington, DC 20375